REMARKS

Status of the Claims

Claims 31, 32, 35-37, 39-41 and 43-69 and 72, and 74-78 are pending in the application. Claim 73 has been canceled without prejudice to future prosecution.

The claims have been rejected, in various combinations, under 35 U.S.C. § 102(B), 35 U.S.C. § 103, 35 U.S.C. § 112, first paragraph, and 35 U.S.C. § 112, second paragraph. Each of these rejections is addressed below in the order presented by the Examiner.

The Examiner's indication that dependent claims 35-37, 41, and 66 would be allowable if rewritten in independent form to include all of the elements of the base claim is acknowledged and appreciated.

Rejection of the claims under 35 U.S.C. § 102

Claims 31-32, 39-40, 43-44, 64-65, 72 and 74-76 are rejected as allegedly anticipated by Takagi *et al.*, *J. Biol. Chem.* 264:6017-6020 (1989) ("Takagi *et al.*"). In making this rejection, the Examiner alleges that the vWF propolypeptide (ppvWF) was known in the art and concludes that there is no reason to believe that the ppvWF preparation of Takagi *et al.* is contaminated with active viruses, *i.e.*, that the ppvWF preparation of Takagi *et al.* inherently has the same properties of the presently claimed pro-vWF compositions. Applicants respectfully traverse.

To anticipate a claim, a single prior art reference must disclose each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987) and *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

It is well settled that an Examiner has the burden of providing a rationale or some evidence to support a rejection based on inherency. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of

the applied prior art." (MPEP § 2112(IV), citing *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

Moreover, the evidence provided "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. . . . Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing ***may*** result from a given set of circumstances is not sufficient." (MPEP §2112; citing *In re Robinson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999) (emphasis added)).

In the present rejection, the Examiner provides little reason or evidence to support the rejection. There is no discussion or evidence to show that any of the steps (*e.g.*, column chromatography and dialysis) used to make the ppvWF preparation of Takagi *et al.*, were or could be effective in eliminating or inactivating any contaminating viruses, thus rendering the ppvWF suitable for therapeutic administration. As discussed above, the Examiner must provide evidence or reasoning that shows that the allegedly inherent characteristic (*i.e.*, suitability for therapeutic administration because of the minimal risk of viral contamination) ***necessarily*** flows from the teachings of the applied prior art.

In alleging that the presently claimed pro-vWF preparation is anticipated by Takagi *et al.*, the Examiner states that Applicants have provided no evidence comparing the ppvWF preparation of Takagi *et al.* and the presently claimed pro-vWF preparation. As noted above, the Examiner has the burden to show that the ppvWF preparation of Takagi *et al.* is suitable for therapeutic administration. Thus, the rejection is improper.

However, as discussed in detail below, such evidence is unnecessary to demonstrate that the presently claimed pro-vWF preparation is patentably distinguishable from the ppvWF preparation of Takagi *et al.* In support of this position, Applicants present a Declaration of Dr. Peter Turacek under 37 C.F.R. § 1.132. As clarified by Dr. Turacek, issue is not whether the ppvWF preparation of Takagi *et al.* does indeed contain viruses, but rather, whether it could be contaminated with viruses (*see*, Declaration ¶8). There is a striking difference in the risk of viral contamination associated with the presently claimed pharmaceutical

preparation of provWF and the ppvWF preparation described in Takagi *et al.* (*see*, Declaration ¶8). Dr. Turacek explains the serious medical risk of contamination associated with the ppvWF preparation of Takagi *et al.*, is such that a skilled person, *i.e.*, a physician, would not consider the ppvWF preparation of Takagi *et al.* to be suitable for therapeutic administration (*see*, Declaration ¶¶ 7 and 8). The high medical risk is minimized in the presently claimed pro-vWF preparations by viral inactivation procedures.

As explained by Dr. Peter Turecek in his Declaration, it is well settled in the art that there is a serious medical risk that blood and blood products are contaminated with viruses and that viral inactivation procedures are required to render blood products suitable for therapeutic use (*see*, Declaration ¶¶ 6, 7, and 8). Numerous scientific references provided by Dr. Turecek reflect the state of understanding in the art that without viral inactivation or elimination treatments, blood products are not suitable for therapeutic administration (*see*, Declaration ¶ 6 for a discussion of Remington *et al.*, *Vox Sang.* 87(1):10-8 (2004); Jackson, *Br. J. Biomed. Sci.*, 60(4):227-32 (2003); and European Agency for the Evaluation of Medicinal Products (EMEA), *Note for Guidance on Assessing the Risk for Virus Transmission - New Chapter 6 of the Note for Guidance on Plasma-derived Medicinal Products* CPMP/BWP/5180/3 (2003)). The references discuss the issue of viral contamination in blood products and emphasize the importance of treating blood products with viral elimination and inactivation procedures to minimize the risk viral contamination so that the blood products are suitable for therapeutic administration (*see*, Declaration ¶ 6). Dr. Turacek notes that multiple health authorities (*e.g.*, the EMEA and the World Health Organization ("WHO")) have provide advice to minimize the risk of viral contamination for plasma derived medicinal products, *e.g.*, both the EMEA and WHO advise that virus removal and inactivation steps should be included in the manufacture of blood products so that they are suitable for therapeutic administration (*see*, Declaration ¶6). Therefore, based on what is known in the art and as confirmed by Dr. Turecek, one of skill in the art would appreciate that it is essential that blood products are subjected to viral elimination or inactivation procedures, to minimize the risk of viral contamination and render them suitable for therapeutic administration as required by the present claims.

Takagi *et al.* does not describe a pro-vWF preparation that has a minimal risk of viral contamination and is, accordingly, suitable for therapeutic administration. As Dr. Turecek explains, Takagi *et al.* describes preparation of ppvWF by passing sonicated platelet concentrates through a series of purification columns (*i.e.*, a collagen column, an organomercurial-agarose column, and a lectin-agarose column), none of which eliminate or inactivate viruses so that the ppvWF is suitable for therapeutic administration (*see*, Declaration ¶ 7(a)-(e)). Dr. Turacek clarifies that the collagen column captures collagen-binding blood coagulation factors (*e.g.*, ppVWF) in the platelet concentrates, the organomercurial-agarose column eliminates proteins with free SH groups, and the lectin agarose column captures glycoproteins such as ppvWF and that none of these columns inactivate or eliminate viruses (*see*, Declaration ¶ 7(b)-(e)). Takagi *et al.* also does not describe ***any*** art-recognized procedures (*e.g.*, pasteurization, photochemical treatment, methylene blue treatment, solvent detergent treatment, and caprylate treatment) to eliminate or inactivate viruses from the platelet concentrates or from any of the column eluates (*see*, Declaration ¶¶ 6 and 7(e)). As discussed above and explained by Dr. Turecek, in the absence of any steps to eliminate or inactivate viruses, any viruses present in the platelet concentrates would also contaminate the final ppvWF preparation of Takagi *et al.* (*see*, Declaration ¶¶ 6 and 7(e)). Therefore, it does not ***necessarily*** flow from the teachings Takagi *et al.*, that viruses have been inactivated or eliminated from the ppvWF preparation and Takagi *et al.* does not describe the presently claimed preparation of pro-vWF that is ***suitable for therapeutic administration***. Given the impossibility for anyone to establish that the criteria for inherent anticipation are met, there is no precedent for shifting the PTO's burden of proof to the applicants in the instant case. In the absence of such facts, the burden of establishing inherent anticipation is not met. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 102(b).

Rejection of the claims under 35 U.S.C. § 103(a):

Claims 31, 32, 39, 40, 43-44, 64-65 and 72 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Takagi *et al.* in view of EP 131740 to Neurath ("Neurath") and Blann *et al.*, *Eur. J. Vasc. Surg.* 8:10-15 (1994) ("Blann *et al.*"). The Examiner has alleged that one of skill in the art would have been motivated to combine the teachings of Takagi *et al.* and Neurath *et al.* based on the suggestions of Blann *et al.* Applicants respectfully traverse.

As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, there must be a reasonable expectation of success, and the prior art reference (or references when combined) must teach or suggest all the claim elements.

As an initial matter, Applicants note that the rejection of the claims under 35 U.S.C. § 102(b) discussed in detail above is inconsistent with the rejection under 35 U.S.C. § 103. In making this rejection of the claims under 35 U.S.C. § 103, the Examiner indicates that the disclosure of Tagaki *et al.* and Neurath *et al.* must be combined to disclose all elements of the presently claimed invention. Therefore, the Examiner is acknowledging that the disclosure of Takagi *et al.* does not contain all of the elements of the presently claimed invention, *i.e.*, the Examiner has acknowledged that the ppvWF preparation of Takagi *et al.* and the presently claimed pro-vWF preparations ***are*** distinguishable.

As discussed in detail below, there is no motivation for one of skill in the art to combine the cited references. Moreover, even if one of skill in the art did combine the cited references, there would be no reasonable expectation of success in obtaining the presently claimed pro-vWF preparations.

A. There is No Motivation to Combine the Cited References

In making this rejection, the Examiner has alleged that Blann *et al.* sets forth a causal role for vWF in atherosclerosis, that Takagi *et al.*, disclose that vWF and pro-vWF have opposite physiological effects and concludes that Blann *et al.* supplies the skilled artisan with

motivation to use the viral inactivation of methodology of Neurath *et al.* to treat the ppvWF preparation of to remove contaminating viruses and generate a ppvWF preparation suitable for therapeutic use. The Examiner asserts that Blann *et al.* speculates that vWF is a causal factor in atherosclerosis and provides motivation for one of skill in the art to treat a ppvWF preparation so that it is suitable for therapeutic administration.

However, a perusal of Blann *et al.* reveals that, at most, the reference ***speculates*** that pro-vWF has some role in atherosclerosis and provides an invitation for one of skill in the art to experiment. For example, the paragraph bridging pages 12-13 merely states that raised vWF ***may*** be a marker for atherosclerosis, but does not disclose or suggest that elevated vWF is a cause for atherosclerosis. Similarly, the middle and last paragraphs at col. 1 on page 13 state that it ***may*** be the case that elevated levels of vWF "somehow predispose to, or promote atherosclerosis" and conclude that further studies are needed to explain the raised level of vWF and its possible association with disease, but does not disclose or suggest any specific role for vWF in atherosclerosis. Finally, the last paragraph of page 13 states that vWF ***may*** be used as a "tool for clinical evaluation," and ***speculates*** what the potential outcome of further studies ***may be*** that treatment may comprise a reduction in vWF levels, but does not disclose or suggest any actual role for vWF in atherosclerosis. At most these disclosure are an invitation for one of skill in the art to experiment to determine the actual role of vWF in atherosclerosis.

It is important to note that the disclosure of Blann *et al.* also contains actual ***clinical evidence*** that vWF is not a causal factor in atherosclerosis. For example Blann *et al.* discloses vWF is no higher in patients with multiple atherosclerotic lesions than in patients with a single atherosclerotic lesion (*see*, page 13, col. 1, first paragraph), suggesting that vWF is, in fact, merely a marker and not a causal factor. Blann *et al.* also discloses that atherosclerosis has been reported in patients with von Willebrand disease (*i.e.*, patients lacking or having low levels of vWF) (*see* page 13, col. 1, middle paragraph). Therefore, the based on the entire disclosure of Blann *et al.*, one of skill in the art would not conclude that vVWF was a causal factor in atherosclerosis and would not be motivated to treat atherosclerosis by lowering vWF levels.

Accordingly, on of skill would not be motivated to produce a preparation of pro-vWF that was suitable for therapeutic administration (*i.e.*, a preparation treated to remove or inactivate viruses).

B. Even If One Of Skill In The Art Were To Combine The Disclosures Of The Cited References, The Present Inventors have Demonstrated a Surprising Effect of pro-vWF

In making this rejection, the Examiner has alleged that Takagi *et al.* discloses that ppvWF counteracts mature vWF, that Blann *et al.* suggests that treatment of atherosclerosis could involve lowering vWF levels, and concludes that it would have been obvious to generate a ppvWF preparation suitable for therapeutic administration to a patient with atherosclerotic lesions.

The present invention is based on the surprising discovery that, contrary to the disclosure of Takagi *et al.*, pro-vWF does not counteract the effects of vWF, indeed, pro-vWF ***promotes*** vWF-associated coagulation. The presently claimed pro-vWF preparations are, therefore, useful for treating blood coagulation disorders.

The contribution of pro-vWF to vWF-associated coagulation was determined in three separate sets of *in vitro* and *in vivo* experiments, all of which are set forth in the specification as filed (*see, e.g.* page 4, second paragraph and Examples 1-3 on pages 11 through 13). The first set of experiments is described in Example 1 of the specification (*see*, page 11, sixth paragraph to page 12, third paragraph and Figure 1). Plasma from a patient with severe vWF disease (*i.e.* a patient lacking vWF) was reconstituted with Factor VIII:C and incubated with platelets from a patient with severe vWF disease. Either Factor eight inhibitor bypassing activity ("FEIBA") or Factor VIIa were used to activate the coagulation reaction. A preparation comprising vWF and a high or a low concentration of pro-vWF was added to the constituted plasma and thrombin generation (*i.e.*, clot formation) was monitored. Thrombin generation was observed with both vWF/pro-vWF preparations, with a higher level of thrombin generation observed in following addition of the preparation comprising a higher concentration of pro-vWF.

The second set of experiments is described in Example 2 of the specification (*see*, page 112 fourth and fifth paragraphs and Figure 2). Plasma from a patient with severe vWF

disease (*i.e.* a patient lacking vWF) was reconstituted with Factor VIII:C and incubated with platelets from a patient with severe vWF disease. Either Factor eight inhibitor bypassing activity ("FEIBA") or Factor VIIa were used to activate the coagulation reaction. Preparations comprising increasing concentrations of pro-vWF were added to the constituted plasma and thrombin generation (*i.e.*, clot formation) was monitored in the presence and absence of vWF. Increased thrombin generation was observed with increased concentrations of pro-vWF.

The third set of experiments is described in Example 3 of the specification (*see*, page 12, sixth paragraph to page 13, third paragraph and Figure 3). A vWF deficient canine was infused with a composition comprising pro-vWF and vWF. 95 hours later, the canine was infused with a vWF preparation. Plasma samples taken prior to, during, and post each of the infusions were analyzed for thrombin generation potential as described in paragraph 10 above. An increase in thrombin generation potential was observed during and after infusion with pro-vWF, but was not observed during and after administration of vWF alone.

Taken together, the teachings of the specification unequivocally demonstrate that pro-vWF ***enhances*** vWF-associated thrombin generation in a dose dependent manner. This is in direct contrast to the disclosure of Takagi *et al.* indicating that the physiological activity of pro-vWF is ***inhibition of*** vWF activity (*i.e.*, by inhibiting collagen-induced platelet aggregation). In view of the Applicants' surprising discovery that pro-vWF ***induces*** clot formation, administration of a pro-vWF preparation to patients with atherosclerotic lesions as suggested by the Examiner would exacerbate lesion formation. Therefore, the presently claimed pro-vWF preparations have a surprising property and the presently claimed invention is non-obvious and patentable over the cited art.

Accordingly, Applicants request withdrawal of this rejection under 35 U.S.C., § 103.

Claim Rejections under 35 U.S.C. 112, First Paragraph

Claims 77 and 78 are rejected because the specification allegedly does not describe how to obtain pro-vWF solutions that contain at least 10 nM or at least 100 nM pro-vWF. Applicants respectfully traverse.

As set forth in MPEP § 2164.01, a particular claim is enabled by specification if the specification, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without undue experimentation. A patent need not teach, and preferably omits what is well known in the art (*see, In re Buchner*, 929 F.2d 660, 18 USPQ 2d 1331 (Fed. Cir. 1991) and *Hybritech Inc. v. Monoclonal Antibodies* (Fed. Cir. 1986).

In the instant case, the specification provides ample guidance for one of skill in the art to make the claimed pro-vWF preparations. In particular, the specification at page 4, last paragraph to page 5, first paragraph provides ample guidance for one of skill in the art to purify any desired concentration of pro-vWF. Exemplary methods of pro-vWF purification include, *e.g.*, ion exchange chromatography, affinity chromatography using suitable affinity agents (*e.g.*, monoclonal antibodies, heparin, collagen, or Factor VIII protein) or by gel filtration.

In addition, the specification discloses several references that demonstrate that, at the time the application was filed, it was a routine matter in the art to purify pro-vWF. As previously noted, Fischer *et al.*, *FEBS Lett.* 351:345 (1994) (Fischer *et al.*) and Megan *et al.*, *Thromb. Haemost* 59:364 (1998) (Megan *et al.*), two references disclosed in the instant specification, describe methods that could be used to prepare compositions having at least 10 or 100 nM pro-vWF. The Examiner has alleged that the Fischer *et al.* is directed to a method of expressing full-length vWF in CHO cells and that Megan *et al.* is directed to purification of a FVIII/vWF complex from plasma. A perusal of these references, however, reveals that each reference describes art recognized methods that could be used for purifying pro-vWF. For example, Fischer *et al.* describes expression and isolation of vWF proteins (*i.e.*, pro-vWF and mature vWF) using standard recombinant DNA technology. Fischer *et al.* at page 347, col. 1, second paragraph and page 348, col. 1, first paragraph indicates that pro-vWF was indeed isolated from the expression system described in the reference. Megan *et al.* describes affinity

purification of Factor VIII:vWF complexes from human plasma using a monoclonal antibody that specifically binds to vWF as well as methods for identifying such monoclonal antibodies.

Thus, it is clear from the guidance in the specification and what was known in the art at the time the application was filed, that it was a routine matter to purify pro-vWF preparations comprising at least 10 nM or at least 100 nM. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections under 35 U.S.C. 112, Second Paragraph

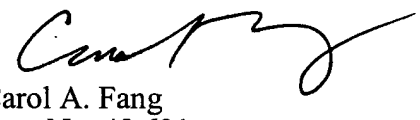
Claim 73 is rejected as allegedly indefinite because it is dependent on a canceled claim. In accordance with the Examiner's suggestion, claim 72 has been canceled without prejudice to future prosecution. Accordingly, Applicants respectfully request withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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